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Clinical paper

Effect of estimated glomerular filtration rate (eGFR) on incidence of out-of-hospital cardiac arrests: A case-control study



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Abstract

Objectives: Serum creatinine levels in the post-resuscitative state have been associated with poor prognosis for out-of-hospital cardiac arrest (OHCA). Several studies have focused on kidney dysfunction in the general population, and the results suggested that serum creatinine level elevation or reduction of the estimated glomerular filtration rate (eGFR) are associated with increased risk of death and cardiovascular events. However, it is uncertain whether the serum creatinine levels or eGFR of OHCA patients are related to the incidence of OHCA. The aim of this study was to determine the association between eGFR and the incidence of OHCA.

Methods: This study was a case-control study performed using the Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiologic Surveillance (CAPTURES) project dataset and the Korea National Health and Nutrition Examination Survey (KNHANES) dataset. Cases were defined as emergency medical service-treated adult OHCA patients with presumed cardiac etiology collected from the CAPTURES dataset. Four controls from the KNHANES dataset were matched to one case based on age, gender, and county. Multivariable conditional logistic regression analysis was conducted to evaluate the effect of eGFR on the incidence of OHCA.

Results: A total of 1211 matched case-control pairs were included in the study analysis. We classified eGFR into 6 categories (≥ 90 , 60–89, 45–59, 30–44, 15–29, and < 15 mL/min/1.73 m²) according to the chronic kidney disease stage. Subjects with an eGFR ≥ 90 mL/min/1.73 m² were used as the reference group. In both the unadjusted and adjusted models, lower eGFR was significantly associated with OHCA incidence. The odds ratio (OR) for OHCA incidence increased sharply as the eGFR declined; the adjusted OR (95% CI) for OHCA incidence was 4.09 (2.81–5.95) with an eGFR of 60–89 mL/min/1.73 m², 36.59 (22.24–60.21) with an eGFR of 45–59 mL/min/1.73 m², 55.26 (29.66–102.94) with an eGFR of 30–44 mL/min/1.73 m², 89.65 (37.25–215.79) with an eGFR of 15–29 mL/min/1.73 m², and 241.87 (73.49–796.01) with an eGFR of less than 15 mL/min/1.73 m².

Conclusion: In this study, we observed an association between reduced eGFR and the risk of OHCA incidence in a large, community-based population. Future prospective studies are needed to better understand how reduced renal function is associated with OHCA occurrence as well as the impact of intensive risk management and intervention of renal function on OHCA incidence.

Keywords: Out-of-Hospital cardiac arrest, Incidence, Glomerular filtration rate, Case-control studies

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<https://doi.org/10.1016/j.resuscitation.2019.06.291>

Received 17 March 2019; Received in revised form 9 June 2019; Accepted 23 June 2019

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Introduction

Out-of-hospital cardiac arrest (OHCA) is a great public health burden due to its high incidence and low survival rate as well as the potential for irreversible neurological and functional disability.^{1,2} Despite the progression of modern resuscitation science, the OHCA survival rate has remained largely unchanged for decades. One study reported that the OHCA survival rate has been static for almost 30 years.³ Another study showed that the overall survival-to-hospital-discharge rates for Pan-Asian OHCA patients were 0.5%–8.5%.⁴ From this aspect, identification of high-risk subjects and treatable risk factors will help to prevent sudden cardiac death and reduce the public health burden.

Cardiac arrest can be considered a model of systemic ischemia and reperfusion that affects all end organs including the kidneys. Several studies on OHCA patients have focused on renal function after cardiac arrest and the results showed that changes in serum creatinine levels after OHCA were associated with patient outcomes.^{5–7} Furthermore, previous studies focused on kidney dysfunction in the general population suggested that elevation in serum creatinine levels and reduction of the estimated glomerular filtration rate (eGFR) are associated with increased risk of death and cardiovascular events.^{8–12} Chronic kidney disease (CKD), diagnosed based on the glomerular filtration rate calculated from serum creatinine, is a well-known risk factor for cardiovascular disease.^{13–17} However, it is uncertain whether eGFR is related to the incidence of OHCA. The aim of this study was to determine the association between eGFR and the development of OHCA.

Methods

Study design and data sources

This study was a case-control study using the Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiologic Surveillance (CAPTURES) project dataset and the Korea National Health and Nutrition Examination Survey (KNHANES) dataset. Cases were obtained from the CAPTURES project dataset and controls were obtained from the KNHANES dataset. Controls were randomly matched according to age (10-year intervals), gender, and county. Matching controls from the same county ensures that the controls are representative of the same source population as the patients. The ratio of controls to patients was 4:1; this ratio was employed to increase the statistical power of the study given the infrequent nature of the event.¹⁸

The CAPTURES project database was created from a nationwide prospective multicenter cohort study designed to identify substrate and triggering risk factors of OHCA based on pathophysiology and implement an emergency department (ED)-based OHCA surveillance system in South Korea. The CAPTURES project was conducted from February 2014 to January 2015 at 27 level-1 EDs. Data for the project were collected from emergency medical service (EMS)-treated OHCA patients judged to possess a cardiac etiology by emergency physicians in each ED. The project excluded patients with terminal illnesses or in hospice care, pregnant patients, those living alone or homeless without a reliable information source, and patients with a 'Do Not Resuscitate' card. OHCA patients for whom resuscitation was not attempted at EDs, those transferred between hospitals, and patients with non-cardiac etiology, including trauma, drowning, poisoning, burns, asphyxia, or hanging were also excluded.

The CAPTURES registry includes socio-demographic information, health behaviors, past medical history, physical and emotional stress, EMS and ED information presented using the Utstein template, laboratory tests, and cardiac examination. Emergency physicians at each study ED collected the information using structured survey papers during a face-to-face interview with the patients' family. Study coordinators at each study ED collected the results of laboratory tests and cardiac examinations via medical record review. The collected data were inputted and transferred to the central data server at the Korea Centers for Disease Control & Prevention (KCDC). The project quality management committee (QMC), which consisted of emergency physicians, cardiologists, and statisticians, reviewed the quality of the data via monthly meetings. The QMC tutored study coordinators before the project began and guided surveys to ensure precise information was collected. When study coordinators were unable to define a coding element, they consulted the emergency physicians in the QMC for clarification.

Community-based controls were selected based on data from the KNHANES conducted from 2008 to 2015. The KNHANES is a national surveillance system based on the National Health Promotion Act conducted annually to assess the health and nutritional status of Koreans since 1998. This nationally representative cross-sectional survey conducted by the KCDC, contains data for approximately 10,000 individuals each year as a survey sample and collects information on socioeconomic status, health-related behaviors, quality of life, healthcare utilization, anthropometric measures, biochemical and clinical profiles for non-communicable diseases, and dietary intakes with three components of the surveys: health interview, health examination, and nutrition survey.¹⁹

Study setting

The Korean EMS is a single tier system that offers a basic to intermediate level of life support ambulance services based in fire stations, run by the fire department and provided for by the government. It serves a population of 50 million from 16 provincial headquarters with 1352 ambulances in 2016. Prehospital providers are classified into level-1 and level-2 emergency medical technicians (EMT), comparable to EMT-intermediate and EMT-basic in the United States, respectively. Even if instructed by medical practitioners, EMTs cannot legally perform blood tests in the field with the exception of blood sugar tests, and point-of-care testing equipment is not available for Korean EMS. If there is no return of spontaneous circulation after at least 5 min of cardiopulmonary resuscitation (CPR), EMTs transport the patient to the closest ED while continuing CPR during transport. Thus, nearly all OHCA patients in Korea are transported to the closest ED. The government designates EDs as levels 1 to 3 depending on the capability and capacity of the facility. Level 1 and level 2 EDs must be fully staffed by emergency physicians by law. Generally, blood samples are drawn during the early CPR phase (within 5 min) after arrival at the ED in Korea.²⁰ Detailed information about EMS characteristics, OHCA protocols, and ED characteristics has been reported previously.^{21,22}

Outcome measures

The primary outcome was the eGFR calculated from the serum creatinine level. We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to estimate the GFR from the measured serum creatinine level.²³ We classified the eGFR into 6

categories (≥ 90 , 60–89, 45–59, 30–44, 15–29, and < 15 mL/min/1.73 m²) according to the CKD stage.^{24,25} Serum creatinine requires time to accumulate before it can be detected. In this study, serum creatinine levels in patients with OHCA were considered as baseline levels of renal function because of the short time interval between the initiation of CPR and blood sampling.^{26–29}

The CAPTURES registry contains information on age, gender, county, date of cardiac arrest, initial electrocardiogram results (ventricular fibrillation, pulseless ventricular tachycardia, pulseless electrical activity, asystole), response time interval, scene time interval, transport time interval, EMS defibrillation attempt, past medical history (hypertension, diabetes mellitus, dyslipidemia, and chronic liver disease), and health behaviors including smoking (current smoker, ex-smoker, never-smoker, and unknown), alcohol [frequent alcohol consumption (more than twice per week), occasional alcohol consumption (once or twice per week), no alcohol consumption, and unknown], sleeping hours (0–6, 6–8, over 8 h, and unknown), and body mass index (BMI) (10.5–18.4, 18.5–24.9, over 25.0, and unknown) for OHCA patients.

When OHCA patients visited EDs, arterial blood gas analysis (ABGA), and routine laboratory examinations including serum creatinine were conducted as soon as possible. Blood samples were usually collected by EMTs or nurses at the EDs and transported to a central laboratory room, where the blood was examined using commercially available laboratory machines. All laboratories participate in qualification programs such as the CAP (College of America Pathologist) survey.

The KNHANES registry contains variables related to the participants' demographics, social factors, health, nutritional status, and laboratory test components including hemoglobin, platelet count, cholesterol, aspartate transaminase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), and creatinine. According to standardized protocols, all health examination procedures are performed by trained medical personnel and all equipment is calibrated periodically. Blood samples are collected from participants aged 10 years and older to obtain laboratory results. The

laboratory data quality control program monitors laboratory performance to ensure that all analytical values meet acceptable standards of precision and accuracy.¹⁹ The primary outcome of this study was the eGFR calculated from the serum creatinine level obtained from the CAPTURES registry (OHCA group) and KNHANES registry (control group).

Statistical analysis

The demographics of the OHCA patient group and the community control group were evaluated. Categorical variables were analyzed using the chi-square test, and continuous variables were analyzed using the Wilcoxon rank sum test. Continuous variables are presented as the median and 25–75% interquartile range (IQR). For the missing variables for past medical history, health behaviors, and laboratory data, multiple imputations with multivariable proportional logistic regression models were conducted. For the matched case-control dataset, multivariable conditional logistic regression analysis was conducted to estimate the effect of eGFR on the incidence of OHCA, and to calculate the adjusted odds ratios (AORs) and 95% confidence intervals (CIs) after controlling for potential confounders identified in directed acyclic graph models, specifically past medical history, health behaviors (smoking, alcohol, sleeping hours, and body mass index) and laboratory data (hemoglobin, platelet count, total cholesterol, and aspartate transaminase). Sensitivity analysis was performed based on subgroups for reduced eGFR that could be related to chronic renal disease already present in the patients. If total prehospital time is relatively short, it can be assumed that the level of creatinine collected at the hospital is similar to that before cardiac arrest. Similarly, if the pH and potassium levels in the hospital are in a relatively normal range, it can be assumed that the creatinine levels would be similar to the pre-arrest condition rather than reflecting post-cardiac arrest changes. Therefore, we included the short prehospital time group, the group of relatively normal range of

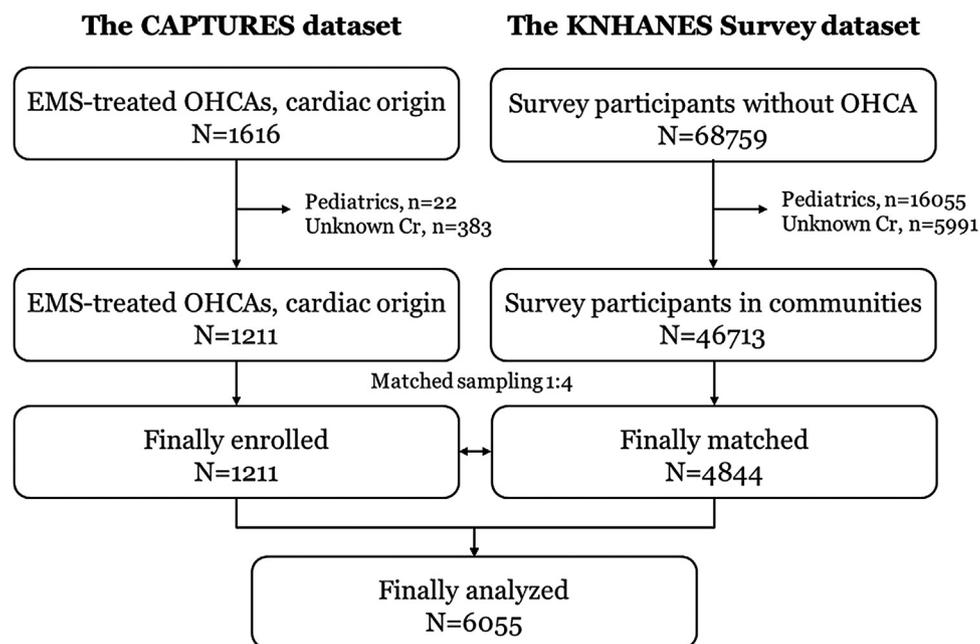


Fig. 1 – Study population flow. CAPTURES: Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiologic Surveillance; KNHANES: The Korea National Health and Nutrition Examination Survey; EMS: emergency medical services; OHCA: out-of-hospital cardiac arrest.

potassium and pH levels, and the group with a relatively younger age without a history of hypertension and diabetes mellitus in the sensitivity analysis. Statistical significance was defined as a P value less than 0.05. All statistical analysis was performed using the SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethics statements

This study was approved by the Institutional Review Board at the research site, and the Korea Center for Disease Control and Prevention (KCDC) approved the use of the data in this study.

Results

A total of 1211 matched case-control pairs were included in the study analysis (Fig. 1). The characteristics of the OHCA patient and community control groups are shown in Table 1. The OHCA patients were more likely to have diabetes mellitus and hypertension and were

less likely to have dyslipidemia. The OHCA patients were also more likely to have lower GFR. Fig. 2 shows eGFR histograms for the OHCA and control groups.

The distribution of laboratory findings for the OHCA patients and community controls is shown in Table 2. The OHCA patients were more likely to have lower hemoglobin levels and higher AST and ALT serum levels than the community controls. Among the OHCA patients, 44.8% had elevated BUN levels, whereas 18.9% of the community controls had elevated BUN levels.

The results of multivariable conditional logistic regression models including adjusted ORs (95% CIs) are shown in Table 3. Subjects with an eGFR ≥ 90 mL/min/1.73 m² were used as the reference group for analysis of the association between the level of the eGFR and each outcome. In both the unadjusted and adjusted models, lower eGFR was significantly associated with OHCA incidence. The odds ratio (OR) for OHCA incidence increased sharply as the eGFR decreased.

Table 4 shows the subgroup analysis results for OHCA patients and community controls. We created subgroups for patients with

Table 1 – Demographics of out-of-hospital cardiac arrest cases and community controls.

	Total (N)	%	OHCA cases (N)	%	Community controls (N)	%	P-value
Total	6055		1211		4844		
Gender							1.00
Female	1890	31.2	378	31.2	1512	31.2	
Male	4165	68.8	833	68.8	3332	68.8	
Age							1.00
19–29	140	2.3	28	2.3	112	2.3	
30–39	280	4.6	56	4.6	224	4.6	
40–49	705	11.6	141	11.6	564	11.6	
50–59	1305	21.6	261	21.6	1044	21.6	
60–69	1020	16.8	202	16.7	818	16.9	
70–	2605	43.0	523	43.2	2082	43.0	
Past medical history							
Diabetes mellitus	984	16.3	317	26.2	667	13.8	<0.01
Hypertension	2244	37.1	539	44.5	1705	35.2	<0.01
Dyslipidemia	741	12.2	82	6.8	659	13.6	<0.01
Smoking							<0.01
Current	2061	34.0	388	32.0	1673	34.5	
Ex-smoker	1452	24.0	226	18.7	1226	25.3	
Never-smoker	2542	42.0	597	49.3	1945	40.2	
Alcohol							<0.01
Frequent	1610	26.6	256	21.1	1354	28.0	
Occasional	2146	35.4	275	22.7	1871	38.6	
Never	2299	38.0	680	56.2	1619	33.4	
Sleeping, hours							<0.01
0–6	1056	17.4	117	9.7	939	19.4	
6–8	3046	50.3	491	40.5	2555	52.7	
8	1953	32.3	603	49.8	1350	27.9	
Body mass index							<0.01
10.5–18.5	245	4.0	80	6.6	165	3.4	
18.5–25	3833	63.3	796	65.7	3037	62.7	
25–50	1977	32.7	335	27.7	1642	33.9	
eGFR, mL/min/1.73 m ²							<0.01
90	1835	30.3	117	9.7	1718	35.5	
60–89	3054	50.4	349	28.8	2705	55.8	
45–59	588	9.7	260	21.5	328	6.8	
30–44	283	4.7	210	17.3	73	1.5	
15–29	161	2.7	146	12.1	15	0.3	
15	134	2.2	129	10.7	5	0.1	

OHCA: out-of-hospital cardiac arrest; eGFR: estimated glomerular filtration rate.

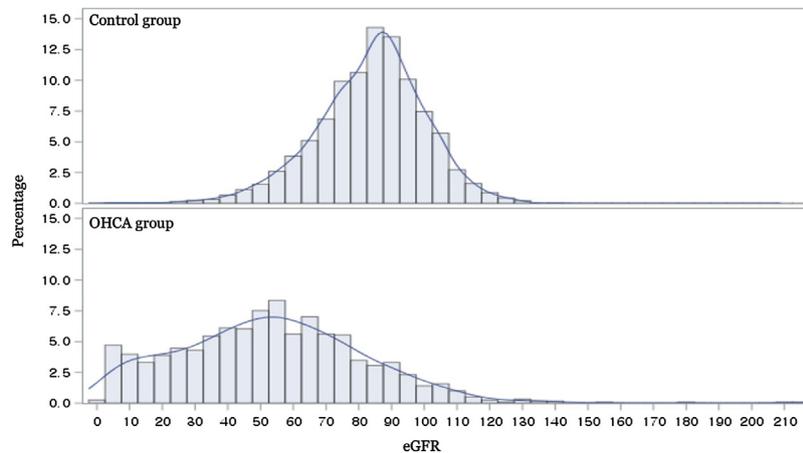


Fig. 2 – Estimated glomerular filtration rates (eGFR) for OHCA and Control groups.

Table 2 – Distribution of laboratory findings of out-of-hospital cardiac arrest cases and community controls.

	Total (N)	%	OHCA cases (N)	%	Community controls (N)	%	P-value
All	6055		1211		4844		
Hemoglobin, g/dL							<0.01
<12	830	13.7	497	41.0	333	6.9	
≥12	5225	86.3	714	59.0	4511	93.1	
Platelet count, × 10 ³ /μL							<0.01
<130	440	7.3	317	26.2	123	2.5	
130–400	5531	91.3	876	72.3	4655	96.1	
≥400	84	1.4	18	1.5	66	1.4	
Cholesterol, mg/dL							<0.01
<200	4180	69.0	1063	87.8	3117	64.3	
≥200	1875	31.0	148	12.2	1727	35.7	
AST, IU/L							<0.01
<40	4787	79.1	204	16.8	4583	94.6	
≥40	1268	20.9	1007	83.2	261	5.4	
ALT, IU/L							<0.01
<40	4995	82.5	412	34.0	4583	94.6	
≥40	1060	17.5	799	66.0	261	5.4	
BUN, mg/dL							<0.01
<10	287	4.7	77	6.4	210	4.3	
10–20	4311	71.2	592	48.9	3719	76.8	
20–50	1302	21.5	390	32.2	912	18.8	
50–100	137	2.3	134	11.1	3	0.1	
≥100	18	0.3	18	1.5	0	0.0	

OHCA: out-of-hospital cardiac arrest; AST: aspartate transaminase; ALT: alanine aminotransferase; BUN: blood urea nitrogen.

Table 3 – Multivariable logistic regression analysis of eGFR for out-of-hospital cardiac arrest incidence.

	OHCA cases/community controls n/n	Unadjusted OR	95% CI	Adjusted OR	95% CI
Total	1211/4844				
eGFR, mL/min/1.73 m ²					
90	117/1718	1.00		1.00	
60–89	349/2705	1.89	1.52–2.36	4.09	2.81–5.95
45–59	260/328	11.6	9.08–14.9	36.6	22.2–60.2
30–44	210/73	42.2	30.5–58.5	55.3	29.7–102.9
15–29	146/15	142.9	81.3–250.9	89.7	37.3–215.8
≤15	129/5	378.8	152.1–943.8	241.9	73.5–796.0

OHCA: out-of-hospital cardiac arrest; eGFR: estimated glomerular filtration rate; OR: odds ratio; CI: confidence interval.

relatively short prehospital time less than 30 min, relatively normal range of serum potassium and pH, and relatively young age with no history of diabetes and hypertension. We also performed the same analysis for patients with an eGFR ≥60, 45–59, and <45 mL/min/

1.73 m² to minimize outlier effects and visualize the gross trend for eGFR. Analysis of the subgroups showed a similar trend: the OR for OHCA incidence increased as the eGFR decreased. Total prehospital time was calculated as the difference between estimated collapse

Table 4 – Sensitivity analysis.

	Short prehospital time (<30 min)		Serum potassium <5.5 pH >7.0		Age <65 Non-DM and Non-Hypertension	
	Number of arrest group = 534		Number of arrest group = 432		Number of arrest group = 351	
	Adjusted OR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
eGFR, mL/min/1.73 m ²						
60	1.00		1.00		1.00	
30–59	10.7	6.82–16.8	11.3	6.91–18.5	133.4	38.9–458.0
29	25.5	15.2–42.7	18.4	10.2–33.5	123.8	15.7–972.8

DM: Diabetes mellitus; eGFR: estimated glomerular filtration rate.

time and ED visit time. In the relatively short prehospital time group, the average prehospital time was 20.3 min (median: 22 min (25% percentile 17 min- 75% percentile 26 min)).

Discussion

This case-control study found that decreased eGFR was associated with an increased OR, i.e. a relative risk of OHCA incidence. The effect of relative eGFR risk on cardiac arrest sharply increased as eGFR decreased after adjusting for past medical history, health behaviors, and laboratory data. We observed a nonlinear relationship between the eGFR and the risk of OHCA incidence, which further rose sharply when the values of eGFR dropped below 60 mL/min/1.73 m².

In clinical practice, estimations of renal function using serum creatinine and eGFR are commonly performed.²⁶ Elevation of the serum creatinine level is associated with the deterioration of kidney function, acute kidney injury (AKI), and CKD. In this study setting, elevated serum creatinine level and decreased eGFR in OHCA patients suggested the presence of CKD in the patients. Because serum creatinine is an amino acid derived from the non-enzymatic conversion of creatine, it requires time to accumulate before it can be detected in serum.^{27–29} The half-life of creatinine in normal subjects varies between 2.4 and 3.85 h and is prolonged as renal function worsens.³⁰ One study showed that serum creatinine increases by 50% after 4 h with no preexisting CKD, whereas it takes 23 h to achieve a 50% increase in serum creatinine for a patient with stage 4 CKD.²⁶ The OHCA patients in this study were in the creatinine clearance cessation state (e.g., AKI with anuria). Since blood samples were collected as soon as possible, the serum creatinine levels of the OHCA patients can be considered to represent the baseline levels of renal function. In this regard, increased serum creatinine levels and corresponding reduced eGFR may be indicative of CKD.

Some studies focused on changes in the kidney functions of OHCA patients after cardiac arrest and found that these changes were associated with the prognosis of cardiac arrest.^{5–7} However, these studies did not show an association with cardiac arrest incidence or identify the risk factors of cardiac arrest. Other studies focused on chronic kidney dysfunction estimated from serum creatinine level or eGFR with cardiovascular disease.^{8–12,31,32} These studies have limitations because they target patients with stable CKD, who are routinely followed with frequent measurements of creatinine levels or eGFR.

Subgroup analysis revealed that the association of reduced eGFR with OHCA incidence is generally applicable to public populations.

The subgroup of relatively short prehospital time, which may minimize the influence of the cardiac arrest on serum creatinine level also represents similar effects of eGFR on OHCA incidence. Generally, if the cardiac arrest time is extended, the pH of the hospital blood test is low and potassium is high. If these values are in a relatively normal range, creatinine reported in the same blood may probably reflect the situation before the cardiac arrest. Relatively young patients (Age <65) who had no diabetes and hypertension showed a higher odds ratio of eGFR on OHCA incidence among subgroups. Even if sensitivity analysis excluded the effects of age and other underlying diseases, low kidney function seems to be closely related to the high incidence of out-of-hospital cardiac arrest. These results imply the importance of serum creatinine surveillance of the population. With the prevalence of kidney disease steadily increasing temporally, intensive risk management and more effective interventions are needed to reduce the burden of cardiovascular complications of kidney disease as well as kidney disease itself.

There are some limitations to this study. First, there was a lack of pre-arrest serum creatinine levels to determine the baseline kidney function. Additionally, the influence of CPR on serum creatinine levels and eGFR is uncertain, i.e. these variables can be representative of any time course during kidney function deterioration. This limitation, however, can be overcome because of the short time interval between the initiation of CPR and the acquisition of serum samples for the OHCA patients in this study setting. As mentioned earlier, serum creatinine requires time to accumulate before it can be detected. Therefore, we can assume the creatinine levels for all OHCA patients in this study represent the baseline serum levels. Second, because the study was a case-control study, there might be biases that were not controlled. The control group was randomly matched according to age, gender, and county, which are representative of populations at risk. However, there is some possibility of misclassification. Third, the case and control groups had different study timeframes. Patient data were collected from 2014 to 2015 while controls were enrolled from 2008 to 2015. This difference could be a potential biasing factor. Finally, prospective studies are required to identify the effect of kidney dysfunction on risk stratification for cardiovascular disease.

Conclusion

This study demonstrated that elevated serum creatinine and the corresponding reduction in eGFR are associated with increased OR, i.e. a relative risk of OHCA incidence, based on multi-center observational data including OHCA patients and the general population. An important strength of this study is the inclusion of a

large sample size from a multicenter hospital-based database and general population survey.

Funding

This study was supported and funded by the Korea Centers for Disease Control and Prevention (KCDC).

Author contributions

Drs. Lim and Jeong had full access to all of the data in the study and take responsibility for the integrity of the data as well as the accuracy of the data analysis.

Study concept and design: Drs. Lim, Shin, and Jeong

Acquisition, analysis, or interpretation of data: Drs. Ro and Jeong,

MPH Kim

Drafting of the manuscript: Dr. Lim

Critical revision of the manuscript for important intellectual content:

Drs. Jeong, Ro, and Shin

Statistical analysis: Dr. Ro

Obtained funding: Dr. Shin

Administrative, technical, or material support: Drs. Ro, MPH Kim

Study supervision: Drs. Shin and Jeong

Manuscript approval: All authors

Conflict of interest

The Authors declare that there are no conflicts of interest.

Acknowledgement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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